



---

Year: 2020

---

## **Study protocol for an observational study of cerebrospinal fluid pressure in patients with degenerative cervical myelopathy undergoing surgical deCOMPRESSION of the spinal CORD: the COMP-CORD study**

Zipser, Carl Moritz ; Pfender, Nikolai ; Spirig, Jose Miguel ; Betz, Michael ; Aguirre, Jose ; Hupp, Markus ; Farshad, Mazda ; Curt, Armin ; Schubert, Martin

**Abstract:** **INTRODUCTION** Degenerative cervical myelopathy (DCM) is a disabling spinal disorder characterised by sensorimotor deficits of upper and lower limbs, neurogenic bladder dysfunction and neuropathic pain. When suspected, cervical MRI helps to reveal spinal cord compression and rules out alternative diagnoses. However, the correlation between radiological findings and symptoms is weak. Cerebrospinal fluid pressure (CSFP) analysis may complement the appreciation of cord compression and be used for intraoperative and postoperative monitorings in patients undergoing surgical decompression. **METHODS AND ANALYSIS** Twenty patients diagnosed with DCM undergoing surgical decompression will receive standardised lumbar CSFP monitoring immediately before, during and 24 hours after operation. Rest (ie, opening pressure, CSF pulsation) and stimulated (ie, Valsalva, Queckenstedt's) CSFP-findings in DCM will be compared with 20 controls and results from CSFP monitoring will be related to clinical and neurophysiological findings. Arterial blood pressure will be recorded perioperatively and postoperatively to calculate spinal cord perfusion pressure and spinal vascular reactivity index. Furthermore, measures of CSFP will be compared with markers of spinal cord compression by means of MR imaging. **ETHICS AND DISSEMINATION** The study protocol conformed to the latest revision of the Declaration of Helsinki and was approved by the local Ethics Committee of the University Hospital of Zurich (KEK-ZH number PB-2016-00623). The main publications from this study will cover the CSFP fluid dynamics and pressure analysis preoperative, perioperative and postoperative correlated with imaging, clinical scores and neurophysiology. Other publications will deal with preoperative and postoperative spinal perfusion. Furthermore, we will disseminate an analysis on waveform morphology and the correlation with blood pressure and ECG. Parts of the data will be used for computational modelling of cervical stenosis. **TRIAL REGISTRATION NUMBER** ClinicalTrials.gov Registry (NCT02170155).

DOI: <https://doi.org/10.1136/bmjopen-2020-037332>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-193518>

Journal Article

Published Version




The following work is licensed under a Creative Commons: Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.

Originally published at:

Zipser, Carl Moritz; Pfender, Nikolai; Spirig, Jose Miguel; Betz, Michael; Aguirre, Jose; Hupp, Markus; Farshad, Mazda; Curt, Armin; Schubert, Martin (2020). Study protocol for an observational study of cerebrospinal fluid pressure in patients with degenerative cervical myelopathy undergoing surgical deCOMPression of the spinal CORD: the COMP-CORD study. *BMJ Open*, 10(9):e037332.  
DOI: <https://doi.org/10.1136/bmjopen-2020-037332>

# BMJ Open Study protocol for an observational study of cerebrospinal fluid pressure in patients with degenerative cervical myelopathy undergoing surgical deCOMPreSSion of the spinal CORD: the COMP-CORD study

Carl Moritz Zipser <sup>1,2</sup>, Nikolai Pfender,<sup>1,2</sup> Jose Miguel Spirig,<sup>2</sup> Michael Betz,<sup>2</sup> Jose Aguirre,<sup>2,3</sup> Markus Hupp,<sup>1,2</sup> Mazda Farshad,<sup>2</sup> Armin Curt,<sup>1,2</sup> Martin Schubert<sup>1,2</sup>

**To cite:** Zipser CM, Pfender N, Spirig JM, *et al.* Study protocol for an observational study of cerebrospinal fluid pressure in patients with degenerative cervical myelopathy undergoing surgical deCOMPreSSion of the spinal CORD: the COMP-CORD study. *BMJ Open* 2020;**10**:e037332. doi:10.1136/bmjopen-2020-037332

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-037332>).

Received 30 January 2020

Revised 31 July 2020

Accepted 06 August 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Department of Neurology and Neurophysiology, Balgrist University Hospital, Zurich, Switzerland

<sup>2</sup>University Spine Center, Balgrist University Hospital, Zurich, Switzerland

<sup>3</sup>Department of Anesthesiology, Balgrist University Hospital, Zurich, Switzerland

## Correspondence to

Dr Carl Moritz Zipser;  
[carlmoritz.zipser@balgrist.ch](mailto:carlmoritz.zipser@balgrist.ch)

## ABSTRACT

**Introduction** Degenerative cervical myelopathy (DCM) is a disabling spinal disorder characterised by sensorimotor deficits of upper and lower limbs, neurogenic bladder dysfunction and neuropathic pain. When suspected, cervical MRI helps to reveal spinal cord compression and rules out alternative diagnoses. However, the correlation between radiological findings and symptoms is weak. Cerebrospinal fluid pressure (CSFP) analysis may complement the appreciation of cord compression and be used for intraoperative and postoperative monitorings in patients undergoing surgical decompression.

**Methods and analysis** Twenty patients diagnosed with DCM undergoing surgical decompression will receive standardised lumbar CSFP monitoring immediately before, during and 24 hours after operation. Rest (ie, opening pressure, CSF pulsation) and stimulated (ie, Valsalva, Queckenstedt's) CSFP—findings in DCM will be compared with 20 controls and results from CSFP monitoring will be related to clinical and neurophysiological findings. Arterial blood pressure will be recorded perioperatively and postoperatively to calculate spinal cord perfusion pressure and spinal vascular reactivity index. Furthermore, measures of CSFP will be compared with markers of spinal cord compression by means of MR imaging.

**Ethics and dissemination** The study protocol conformed to the latest revision of the Declaration of Helsinki and was approved by the local Ethics Committee of the University Hospital of Zurich (KEK-ZH number PB-2016-00623). The main publications from this study will cover the CSFP fluid dynamics and pressure analysis preoperative, perioperative and postoperative correlated with imaging, clinical scores and neurophysiology. Other publications will deal with preoperative and postoperative spinal perfusion. Furthermore, we will disseminate an analysis on waveform morphology and the correlation with blood pressure and ECG. Parts of the data will be used for computational modelling of cervical stenosis.

**Trial registration number** ClinicalTrials.gov Registry (NCT02170155).

## Strengths and limitations of this study

- This interdisciplinary study will provide the first data on cerebrospinal fluid pressure (CSFP) in degenerative cervical myelopathy (DCM) before, during and after surgical decompression.
- There will be a multimodal DCM assessment with clinical scores, quantitative MR imaging, neurophysiology and CSFP analysis.
- This study is the first to perform a digitised measurement and recording of CSFP and invasive arterial blood pressure to derive spinal perfusion pressure (spinal cord perfusion pressure=mean arterial pressure CSFP) in DCM.
- Changes in CSFP may be variable as jugular vein compression (Queckenstedt's test) will be applied manually (by the same investigator) while a pressure cuff for standardisation is technically not applicable.
- Since lumbar CSFP analysis is an invasive technique with usually mild but common side effects, the application of CSFP measurements needs to provide clinically relevant additional diagnostic information to compensate for potential adverse events in patients with DCM.

## INTRODUCTION

### Background

Degenerative cervical myelopathy (DCM) is a common age-related spinal cord disorder characterised by progressive neurological impairment and neuropathic pain.<sup>1,2</sup> With an annual incidence of 2–6 in 100 000 people and 1.6 in 100 000 being surgically treated, these numbers are expected to increase given the ageing of the global population, DCM ranges among the most relevant degenerative spine disorders.<sup>3–5</sup> Most patients are in their sixth decade and present with (asymmetric) sensorimotor and fine-motor deficits of the

upper extremity, gait instability, neurogenic bladder dysfunction, radiating burning and stabbing pain in the upper extremity.<sup>6</sup> Typically, symptoms develop within months, with sometimes subacute aggravation in the natural course or acute exacerbation following trauma. Spinal cord compression arises from degeneration of facet joints and ligaments, disc disease and cervical joint hypermobility. On the microstructural level, segmental blood flow becomes increasingly restricted and microvascular integrity lost, leading to a complex cascade of ischaemia and inflammation, and ultimately, demyelination and neuronal degeneration.<sup>7–9</sup> In some cases, congenital disorders, for example, Down syndrome, Klippel-Feil syndrome and congenital cervical spine stenosis, may accelerate chronic degeneration.<sup>10</sup> Cervical MRI allows the exclusion of differential diagnoses, it may reveal direct signs of myelopathy in some patients, whereas in others, only spinal cord compression and loss of cerebrospinal fluid signal (CSF) may be evident, most common at the levels C5–C6.<sup>11</sup> Various descriptions for cord compression and for degenerative changes are used,<sup>11 12</sup> the correlation to symptoms is reported to be poor by some,<sup>13</sup> whereas other studies report a sufficient correlation.<sup>14</sup> While many asymptomatic patients have disc bulging in cervical MRI, few asymptomatic patients have spinal cord compression or signs of myelopathy.<sup>15</sup> Recently, more sophisticated MR protocols demonstrated higher spinal cord motion at the level of stenosis that correlated with disability.<sup>16</sup> Neurophysiological studies, that is, motor-evoked potential (MEP) and somatosensory-evoked potential (SEP), support the diagnosis and aid in the prognosis of the outcomes,<sup>17</sup> and intraoperative neurophysiologic monitoring can be used to detect imminent spinal cord damage.<sup>18</sup> Contact heat-evoked potentials (CHEPs) may increase the sensitivity of conventional neurophysiology assessments for spinal conduction deficits.<sup>19</sup> Patients with DCM may be treated with conservative management or surgical decompression.<sup>20 21</sup> In patients with moderate or severe disability, current guidelines recommend surgical decompression, with the goal of symptom remission and minimum goal of halting disease progression.<sup>22 23</sup> The decision in favour of surgery over conservative mainly depends on the clinical symptoms and progression and it does not require signs for myelopathy in the MRI.<sup>24</sup> Dorsal and ventral surgical techniques can be chosen, the method depends on the affected structures.<sup>25–29</sup> Perioperative complications may occur in 11%–38% of patients, with higher risk in elder patients with two-stage surgery.<sup>30</sup> Symptoms have a relevant impact on quality of life<sup>31</sup> and improve with timely surgical decompression.<sup>32</sup> Outcomes are generally worse in elderly patients with more severe impairment and longer symptom duration prior to decompression.<sup>33</sup> Therefore, awareness for symptom progression and early diagnosis of DCM is important.<sup>34</sup>

Before the introduction of CT and MRI, cerebrospinal fluid pressure analysis (CSFP) was a common method to quantify spinal cord compression.<sup>35–37</sup> Applying jugular vein compression during lumbar puncture—termed

Queckenstedt's test—leads to an increase in CSFP that is impaired or absent in spinal canal stenosis.<sup>38 39</sup> Also with changing head positions during vein compression, the sensitivity for spinal stenosis may be increased.<sup>38 40 41</sup> The same authors have demonstrated normalised CSFP following decompression in suspected spinal stenosis. MRI to confirm stenosis was not available at that time, however. One study has demonstrated spinal block with CSFP analysis in patients with Arnold-Chiari malformation, which was relieved following laminectomy.<sup>42</sup> In acute spinal cord injury (SCI), it has been found recently that CSFP is altered and restitutes following decompression.<sup>43</sup> Furthermore, a multicentre prospective study estimated spinal cord perfusion pressure (SCPP) from CSFP and mean arterial pressure and found higher SCPP to correlate with improved clinical outcome.<sup>44</sup> From studies that measure intraspinal pressure (ISP) in acute SCI, the spinal vascular reactivity index (sPRx) was calculated, indicating impaired autoregulation in some patients.<sup>45</sup> All these findings support the translation of CSFP measurements to DCM.

In a pilot study, we confirmed feasibility and safety of intraoperative CSFP monitoring at our institution (in press). We were able to demonstrate responsive Queckenstedt's test postdecompression in two patients. Baseline values were not acquired in the pilot study and are subjected to the present study. The optimum SCPP, calculated from overnight recordings of invasive arterial blood pressure (ABP) strongly resembled values obtained in acute SCI patients after decompression.<sup>44</sup>

## Aims and objectives

We aim to explore the potential of dynamic CSFP analysis for intraoperative and postoperative neuromonitoring of decompressive surgery in DCM. We aim to further expand the current knowledge on DCM pathophysiology. The following objectives would allow the achievement of these aims:

The primary objective is evaluating the preoperative, intraoperative and postoperative fluid dynamics of CSFP, including spontaneous pulsations, opening pressure, reaction to jugular vein compression in neutral head position (Queckenstedt's test) and Valsalva manoeuvre.

Secondary objectives are the relation of pressure parameters with clinical and imaging parameters:

1. Investigating CSFP—changes related to perioperative and postoperative complications, for instance, spinal cord swelling and haemorrhage.
2. Correlating preoperative Queckenstedt's test and clinical data (neurological deficits, duration of symptoms, modified Japanese Orthopedic Association scale (mJOA), neurophysiology examinations).
3. Correlating CSFP and structural MRI parameters (spinal cross-section and diameter).
4. Correlating Queckenstedt's test results and blood pressure.

5. Calculating group differences of Queckenstedt's test and Valsalva manoeuvre between control participants and patients with DCM.
6. Investigating CSFP—changes related to body position. Tertiary objectives are the investigation of perfusion parameters:
  1. Determining optimum postoperative SCPP.
  2. Investigating correlations between postoperative sPRx and CSFP.
  3. Calculating differences between perioperative and postoperative SCPP.
  4. Exploring temporal correlations between pressure peaks in CSFP, ABP and ECG.

Our study is novel in several regards. First, previous studies seek to detect spinal compression at times when MRI was not available, whereas this study investigates the relation of structural cord compression and CSF abnormalities. Second, this will be the first study in spinal stenosis that uses the advantages of digitalised measuring and recording. For instance, our approach allows the analysis of waveforms (signals and fast Fourier transformation (FFT) and correlation to ABP as well as the estimation of SCPP. At last, this study first records CSFP during operation and 24 hours after and herewith evaluates its value as a monitoring tool. Our results may increase the physiological understanding of DCM and cerebrospinal fluid dynamics in general.

## METHODS AND ANALYSIS

### Study setting and eligibility criteria

This study will be a single-centre prospective observational study conducted at The University Spine Center Zurich, located at the Balgrist University Hospital, which provides highly specialised treatment for SCI. Pilot data were acquired prior to this study to establish the methodology, refine the study protocol and ensure the cooperation between disciplines involved (neurologists, spine surgeons, anesthesiologists). Enrolment for the study started in December 2019. Reporting followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement, where applicable in the reporting of a study protocol.<sup>46</sup>

Inclusion criteria are clinical symptoms of DCM, radiographic evidence of cervical spinal cord compression, eligibility for surgical decompression, age between 18 and 80 years, written informed consent (IC) and eligibility for CSFP monitoring. Exclusion criteria are contraindications to MRI, for example, cardiac pacemaker, pregnancy (in case of uncertainty, subjects will undergo urine and/or blood testing) and psychiatric disorders that alter ability to give IC or potentially interfere with the measurements.

Control participants should be age-matched and gender-matched and do not have clinical symptoms suggestive of cervical stenosis. They receive bedside lumbar puncture for diagnostic purpose other than stenosis, for example, suspected demyelinating disease and inflammatory

polyneuropathy and CSFP measurement as part of standard procedure.

A total of 20 patients with DCM and 20 patients of control participants will be included in this study, a number was chosen based on the previous CSFP studies in compressive spinal cord disorders. To our best knowledge, three studies compared Queckenstedt's test before and after decompression by two separate lumbar punctures. One study reported six patients with spinal block who underwent decompressive spine surgery, where cord compression was confirmed intraoperatively.<sup>40</sup> Postoperative lumbar puncture revealed normal results. Another study reported spinal block in two patients who later underwent decompressive surgery.<sup>47</sup> Postoperative lumbar puncture showed normal test results. For studying the mechanisms of CSFP abnormalities in Arnold-Chiari malformation preoperative and postoperative, lumbar puncture was performed in nine patients. In all patients, preoperative results were abnormal and normalised after surgery.<sup>42</sup> Although pathology is unlike that suspected in DCM, the number of subjects needed to obtain conclusive results should be similar. Our study is not designed and powered to evaluate the relationship between monitoring results and outcome but as a purely observational study that intends to evaluate CSFP as a potential perioperative monitoring tool.

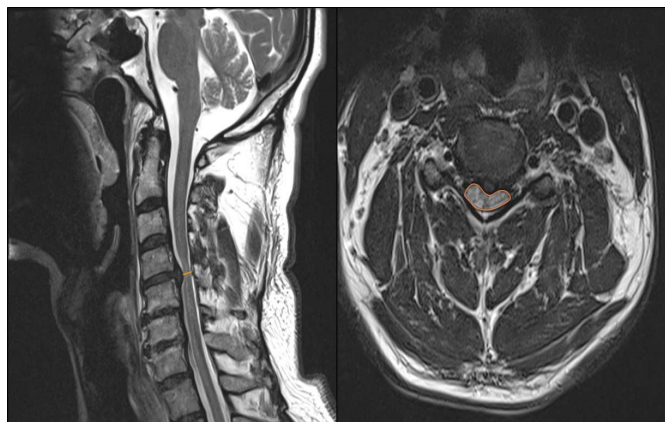
### Ethics and dissemination

The study protocol conformed to the latest revision of the Declaration of Helsinki and was approved by the local Ethics Committee of the University Hospital of Zurich. The main publications from this study will cover the CSFP fluid dynamics and pressure analysis preoperative, perioperative and postoperative correlated with imaging, clinical scores and neurophysiology. Other publications will deal with preoperative and postoperative spinal perfusion. Furthermore, we will disseminate an analysis on waveform morphology and the correlation with blood pressure and ECG. Parts of the data will be used for computational modelling of cervical stenosis.

### Clinical and neurophysiological parameters

In all patients admitted for elective surgery, the Spinal Cord Independence Measure, mJOA, American Spinal Injury Association Impairment Scale and visual analogue scale for pain will be obtained. Additionally, following binary variables will be noted: presence of bladder dysfunction and spasticity. At baseline, a standard set of neurophysiological parameters will be collected: MEP from the lower limbs, tibial F-waves and tibial SEP. Central motor conduction time to the lower extremities will be calculated from F-waves and lumbar stimulation.<sup>48</sup> In patients with contraindications to transcranial magnetic stimulation, for example, cochlear implants and seizures, MEP will not be performed.<sup>49</sup> Additional neurophysiology will be acquired if requested by the investigators. MEP will be acquired with Magstim-200 stimulator connected to a round coil (Magstim Company, Carmarthenshire,





**Figure 1** Cervical sagittal and axial T2w MRI sequences in a representative patient with degenerative cervical myelopathy showing narrowed spinal canal, hyperintense T2w lesions, effacement of the cerebrospinal fluid signal, impression of the spinal cord, and reduced diameter ( $91.55 \text{ mm}^2$ ) at the level of maximum stenosis C4/C5 (orange lines).

Wales, UK) and SEPs with SEPs and F-wave examination with Dantec Keypoint neurophysiology equipment (Natus Medical, San Carlos, USA). In patients scheduled for elective surgery, CHEPs will be acquired (Pathway, Medoc, RamatYishai, Israel). All patients will be followed up 6 months after surgery for neurological examination.

We expect surgical decompression to be performed within a few days after the first consultation in some patients, while other operations are planned weeks before. To account for emergent clinical cases, we defined a minimum data set for inclusion, consisting of preoperative, intraoperative and postoperative clinical examinations, CSFP/ABP monitoring, cervical MRI and mJOA.

### Imaging

All patients who are primarily referred to our Spine Center, which is the majority of patients, will undergo a 3T cervical MRI scan (MAGNETOM SkyraFit, Siemens Healthcare, Erlangen; MAGNETOM Prisma, Siemens Healthcare, Erlangen) including sagittal and axial standard clinical T2w sequences. In patients who underwent recent external MRI, 1.5T cervical is also accepted, if required sequences are included, to avoid repetitive diagnostics. When correlating MRI and CSFP parameters, differences in signal-to-noise ratio between 1.5 and 3T will be considered, respectively. Common quantitative measurements for spinal cord compression are going to be calculated.<sup>12</sup> For characteristic MR findings in DCM, please refer to [figure 1](#).

### Lumbar catheter insertion and CSFP data recording

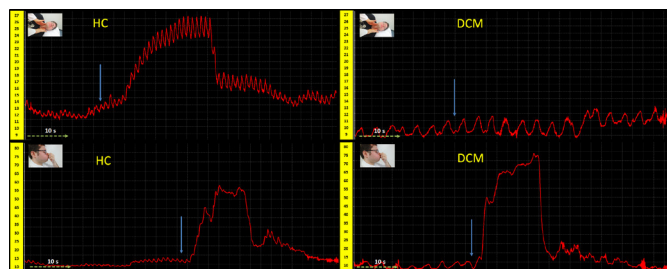
For the purpose of measuring CSFP, a lumbar catheter (Neuromedex Lumbalkatheter 4.5F) will be inserted about 20 cm into the spinal canal through a 14-gauge Tuohy needle in lateral decubital position after narcosis, immediately prior to surgery. Then, it will be connected to an analogue digital pressure converter (Neuromedex VentrEX), and the digitised signal will be linked to a Philips

X2-Pat.Interface+MX 700 Monitor, connected to online recording software ICM+ (University of Cambridge). The correct catheter placement confirmed online by clear response to coughing, respiratory modulation, CSF pulsation or ventilatory-induced Valsalva manoeuvre. The ABP will be recorded concomitantly during and after surgery from a radial artery catheter kept at the same horizontal level as the injured segment of the spinal cord. Additionally, three-lead electrocardiograph will be recorded (ECG).

Based on the established procedures, calculations are as follows: the MAP is calculated from the systolic and diastolic ABP. Then, CSFP and MAP are employed to calculate the SCPP (MAP-CSFP). To further characterise dynamics of spinal perfusion, the sPRx, a measure of spinal cord vascular reactivity will be calculated from the correlation coefficient between mean CSFP and MAP. Before decompression, intraoperatively, we will record CSFP and ABP for 30 min. After surgery, we will record CSFP and ABP up to 24 hours. To calculate perfusion parameters, integrated tools from ICM+ software and established analytical procedures will be used.<sup>45</sup> Perfusion parameters will not be obtained in control participants. Individual and pooled optimum postoperative SCPP (in mm Hg) will be calculated over 6 hours (overnight), estimated by plotting sPRx against SCPP, defining nadir of sPRx as optimum. Additionally, sPRx will be plotted against CSFP to investigate autoregulation capacity.

### CSFP examinations

A standard operating procedure guides the preoperative and postoperative manoeuvres. First, opening pressure will be recorded, followed by Queckenstedt's test in neutral head position ([figure 2](#) shows characteristic findings in the presence of spinal stenosis and normal findings from our recordings). Queckenstedt's test will be performed in lateral decubital position before entering the operation room by applying firm manual pressure on both jugular veins until carotid pulsation was felt for about 10 s. Previous studies reported higher sensitivity of Queckenstedt's test in different head postures, that is, neutral, flexion and extension.<sup>38 40 41</sup> For safety concerns, we will not perform these manoeuvres. Therefore, spinal block might be underdetermined in this cohort. During surgery, CSFP will be recorded without manoeuvres. Intraoperative recording will be performed in supine or prone position, depending on dorsal or ventral surgical approach. After surgery, depending on the time required to extubate and to transfer to intensive care unit, Queckenstedt's test will be performed within 6 hours and >12 hours after surgery. Within these time windows, Valsalva manoeuvre will be performed additionally, if the postoperative level of consciousness allows. Queckenstedt's test >12 hours after surgery will be performed in supine and lateral decubital positions. Queckenstedt's test will be evaluated with regards to maximum amplitude, steepness of slope and return to baseline and frequency spectrum FFT. Independent from the manoeuvres, CSFP, ECG and ABP will



**Figure 2** Bedside CSFP recordings (60 s, x-axes) of CSFP in mm Hg (y-axes) in a patient without (HC; left) and with cervical stenosis (DCM; right). Blue arrows mark the onset of provocation manoeuvres with jugular vein compression (Queckenstedt's test; upper rows) and Valsalva manoeuvre (lower rows), respectively, represented by the pictograms. Upper rows: without stenosis, CSFP was pulsatile (corresponding heart rate around 80 pulses/minute) and rapidly increased from baseline pressure of 12 mm Hg to 27 mm Hg during Queckenstedt's test. In the presence of stenosis, cardiac pulsations were absent, but the signal was still modulated with respiration (corresponding respiratory rate about 18–20/min). Queckenstedt's test was not responsive, that is, CSFP did not react to jugular vein pressure, indicating spinal block. Lower rows: during Valsalva maneuver CSFP increased in both participants to values well above 50 mm Hg. This indicates that different physiological mechanisms are responsible for pressure increase in Queckenstedt's test and Valsalva manoeuvre. Due to more pressure increase with Valsalva test stenosis can be overcome and therefore response is positive in the patient with DCM as well. CSFP, cerebrospinal fluid pressure; DCM, degenerative cervical myelopathy; HC, healthy control.

be recorded continuously up to 24 hours after operation. CSFP examinations will not be performed at follow-up.

To address potential confounding factors that may affect the CSFP analysis, following analyses will be performed. We will compare intraoperative pulsation in patients with dorsal versus ventral surgical approach, that is, prone versus supine body position. Also, postoperative Queckenstedt's test results >12 hours in lateral decubital versus supine body position will be compared.

In controls, lumbar puncture will be performed in lateral decubital position. The pressure transducer will be directly connected to a 20–22-gauge Sprotte or Quincke needle and manoeuvres performed analogously to patients with DCM.

### Data analysis

CSFP-related data are in part purely qualitative, for example, wave morphology, whereas other data are binary, for example, abnormal versus normal reaction after jugular vein compression or continuous, for example, CSFP maximum during Valsalva, jugular vein compression and opening pressure. For the purpose of evaluating preoperative, intraoperative and postoperative pressure indices, descriptive and repeated measurement analysis of variance (ANOVA) including post hoc tests with Bonferroni correction will be performed. For continuous data, general descriptive statistics will be reported as

means and SD. Normal distribution of data will be evaluated with the Kolmogorov-Smirnov test. In case of normal distribution, Student's t-test, otherwise, non-parametric tests will be used to test for group differences (age, sex, pressure indices), maximum amplitudes of Valsalva manoeuvre, and to test preoperative and postoperative maximum Queckenstedt's maximum amplitudes in different body positions. Multiple linear regression analysis will be applied to track the interaction with MAP and the correlation to MRI, clinical, and neurophysiological data. A p value of <0.05 will be considered significant. All analyses will be computed with the Statistical Package for Social Sciences (SPSS, V.25).

### Methodological issues I: CSFP analysis in spinal stenosis

This study has the potential to significantly increase our knowledge on the physiology of DCM and it potentially introduces a method for monitoring intraoperative and postoperative complications. The evaluation of CSFP and especially Queckenstedt's test has a longstanding tradition in the diagnosis of spinal neurological disorders. When reviewers reported about low sensitivity of CSFP for spinal obstruction compared with myelography and intraoperative findings, they mostly referred to lesions at or above the foramen magnum,<sup>50</sup> which is indeed not an ideal subject CSFP analyses.<sup>51</sup> Despite all obstacles,<sup>39</sup> CSFP analysis was considered a useful method for the diagnosis of cervical obstruction before the introduction of myelography. With increasingly sophisticated imaging methods, cervical MRI being considered the gold-standard nowadays, researchers lost interest in CSFP analysis in cervical stenosis. But what can CSFP analysis contribute to the field today? CSFP analysis allows a direct assessment of the CSF compartment and the manipulation of cerebrospinal fluid flow to test local fluid dynamics. The correlation between clinical symptoms and severity of cord compression is controversially debated, with evidence for sufficient correlation<sup>14</sup> and also reports of poor correlation between degree of spinal cord compression as determined in the conventional MRI and individual symptom severity.<sup>13</sup> The physiological understanding of these observations is limited. To overcome this limitation, advanced MRI techniques—aimed at CSF properties—have been developed. In DCM, velocity and flow of CSF have been shown to be decreased,<sup>52 53</sup> and these advanced imaging techniques might be worthwhile additions to routine preoperative investigations. The same is valid for spinal diffusion tensor imaging.<sup>54</sup> However, advanced MRI techniques cannot substitute for CSFP analysis because they measure the flow and velocity only in the resting state, whereas invasive CSFP recordings can be manipulated during measurements. Most importantly, with MRI, an intraoperative monitoring is not feasible and acute postoperative changes are difficult to detect, due to oedema and hardware inserted during the operation.

In summary, CSFP analysis may reveal severe functional spinal obstruction in mild structural compression and therefore complement the diagnostic assessment.



Patients benefit from this approach because it may help discriminate patients who have functionally relevant spinal obstruction and thus may be eligible for operation from those who can be followed up and managed conservatively. Due to its invasive nature, CSFP monitoring is not meant to substitute MRI, but to supplement imaging in some cases. For intraoperative monitoring, it could be combined with established technologies, for example, intraoperative ultrasound.<sup>55</sup>

### Methodological issues II: the evaluation of SCPP with CSFP

The evaluation of spinal cord perfusion is challenging. Due to the thin calibre of the widely distributed spinal vessels, conventional strategies, to assess perfusion, such as MR-/CT-angiography and neurovascular ultrasound, are not applicable. Direct invasive measurement in segmental arteries has been performed previously, but it is very challenging and restricted to the intraoperative setting and therefore does not allow postoperative monitoring.<sup>56</sup> Alternatively, the correlation between MAP and lumbar CSFP has been proposed to estimate spinal cord perfusion in traumatic injury.<sup>43</sup> Animal experiments have indeed proved that CSFP and spinal cord perfusion are interrelated. When CSF was drained in mongrel dogs at the cisterna magna during thoracic aorta occlusion, spinal cord blood flow (SCBF) increased.<sup>57</sup> A study which chose the lumbar CSF route in dogs has shown decreasing SCBF when mock CSF was infused,<sup>58</sup> a finding that could be replicated in the same canine model from another group.<sup>59</sup> Thus, the calculation of SCPP from MAP and lumbar CSFP appears valid for the estimation of postoperative SCBF.

Investigations of SCPP are relevant for defining optimum intraoperative and postoperative blood pressure values. Current guidelines recommend MAP goals of 85–90 mm Hg in acute SCI, as higher MAP correlates with better neurological outcome.<sup>60 61</sup> However, studying MAP does only provide an indirect mean of spinal cord perfusion. In acute SCI, therefore, studies were conducted to measure SCPP, while in DCM, the spinal perfusion has not been investigated in vivo yet. Two approaches were applied in traumatic SCI: with subdural probes at the level of injury, the group of Papadopoulos has demonstrated that ISP is elevated at the site of acute traumatic injury, resulting in reduced perfusion and impaired haemodynamic autoregulation, potentially causing a worse neurological outcome.<sup>45 62–64</sup> With lumbar catheters, the group of Kwon has demonstrated that SCPP >50 mm Hg is a strong predictor for better neurological outcome after acute SCI.<sup>44</sup> Although reasonable arguments in favour of subdural at-level measurements exist,<sup>65</sup> we chose the lumbar estimation for this study for two reasons. First, the dura is not injured in DCM and when introducing a subdural probe, the dura must be opened, and second, because there is substantial evidence on lumbar CSFP analysis that we aim to extend.

### Data statement

Data from pressure analysis may be shared on reasonable request.

**Acknowledgements** We are grateful to our pilot study participants. We would like to thank Mrs Regula Schüpbach and Iris Krüsi for study administration and Matthias Noll for IT support. We would like to thank the assistants and nurses from the intensive care unit, neurophysiology and operating room for their support.

**Contributors** The study concept and design were conceived by CMZ, MS, AC. Recruitment will be performed by CMZ, NP, JMS, MB, MF. Surgical and neurological procedures will be performed by MF, JMS, MB, CMZ, NP, JA. MRI analysis will be performed by NP, MH, CMZ. CSFP analysis will be performed by CMZ. CMZ prepared the first draft of the manuscript. All authors provided edits and critiqued the manuscript for intellectual content.

**Funding** This work will be supported by the Swiss Paraplegic Foundation, Nottwil (CMZ, AC, MS), Switzerland and the Balgrist Foundation (CMZ, MS, MF), Zurich, Switzerland.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

### ORCID iD

Carl Moritz Zipser <http://orcid.org/0000-0002-4396-4796>

### REFERENCES

- 1 Davies BM, Mowforth OD, Smith EK, *et al.* Degenerative cervical myelopathy. *BMJ* 2018;360:k186.
- 2 Badhiwala JH, Ahuja CS, Akbar MA, *et al.* Degenerative cervical myelopathy - update and future directions. *Nat Rev Neurol* 2020;16:108–24.
- 3 Boogaarts HD, Bartels RHMA. Prevalence of cervical spondylotic myelopathy. *Eur Spine J* 2015;24 Suppl 2:139–41.
- 4 Fehlings MG, Tetreault L, Nater A, *et al.* The aging of the global population: the changing epidemiology of disease and spinal disorders. *Neurosurgery* 2015;77 Suppl 4:S1–5.
- 5 Wu J-C, Ko C-C, Yen Y-S, *et al.* Epidemiology of cervical spondylotic myelopathy and its risk of causing spinal cord injury: a national cohort study. *Neurosurg Focus* 2013;35:E10.
- 6 Chiles BW, Leonard MA, Choudhri HF, *et al.* Cervical spondylotic myelopathy: patterns of neurological deficit and recovery after anterior cervical decompression. *Neurosurgery* 1999;44:762–9.
- 7 Kalsi-Ryan S, Karadimas SK, Fehlings MG. Cervical spondylotic myelopathy: the clinical phenomenon and the current pathobiology of an increasingly prevalent and devastating disorder. *Neuroscientist* 2013;19:409–21.
- 8 Liu H, MacMillan EL, Jutzeler CR, *et al.* Assessing structure and function of myelin in cervical spondylotic myelopathy: evidence of demyelination. *Neurology* 2017;89:602–10.
- 9 Yu WR, Liu T, Kiehl T-R, *et al.* Human neuropathological and animal model evidence supporting a role for Fas-mediated apoptosis and inflammation in cervical spondylotic myelopathy. *Brain* 2011;134:1277–92.
- 10 Nouri A, Tetreault L, Singh A, *et al.* Degenerative cervical myelopathy: epidemiology, genetics, and pathogenesis. *Spine* 2015;40:E675–93.
- 11 Nouri A, Martin AR, Tetreault L, *et al.* MRI analysis of the combined prospectively collected AOSpine North America and international data: the prevalence and spectrum of pathologies in a global cohort of patients with degenerative cervical myelopathy. *Spine* 2017;42:1058–67.
- 12 Tempest-Mitchell J, Hilton B, Davies BM, *et al.* A comparison of radiological descriptions of spinal cord compression with quantitative measures, and their role in non-specialist clinical management. *PLoS One* 2019;14:e0219380.
- 13 Hilton B, Tempest-Mitchell J, Davies BM, *et al.* Cord compression defined by MRI is the driving factor behind the decision to operate in degenerative cervical myelopathy despite poor correlation with disease severity. *PLoS One* 2019;14:e0226020.



- 14 Nouri A, Tetreault L, Dalzell K, *et al.* The relationship between preoperative clinical presentation and quantitative magnetic resonance imaging features in patients with degenerative cervical myelopathy. *Neurosurgery* 2017;80:121–8.
- 15 Nakashima H, Yukawa Y, Suda K, *et al.* Abnormal findings on magnetic resonance images of the cervical spines in 1211 asymptomatic subjects. *Spine* 2015;40:392–8.
- 16 Wolf K, Hupp M, Friedl S, *et al.* In cervical spondylotic myelopathy spinal cord motion is focally increased at the level of stenosis: a controlled cross-sectional study. *Spinal Cord* 2018;56:769–76.
- 17 Fujimoto K, Kanchiku T, Imajo Y, *et al.* Use of central motor conduction time and spinal cord evoked potentials in the electrophysiological assessment of compressive cervical myelopathy. *Spine* 2017;42:895–902.
- 18 Takeda M, Yamaguchi S, Mitsuura T, *et al.* Intraoperative neurophysiologic monitoring for degenerative cervical myelopathy. *Neurosurg Clin N Am* 2018;29:159–67.
- 19 Jutzeler CR, Ulrich A, Huber B, *et al.* Improved diagnosis of cervical spondylotic myelopathy with contact heat evoked potentials. *J Neurotrauma* 2017;34:2045–53.
- 20 Rhee J, Tetreault LA, Chapman JR, *et al.* Nonoperative versus operative management for the treatment degenerative cervical myelopathy: an updated systematic review. *Global Spine J* 2017;7:35S–41.
- 21 Tetreault LA, Rhee J, Prather H, *et al.* Change in function, pain, and quality of life following structured Nonoperative treatment in patients with degenerative cervical myelopathy: a systematic review. *Global Spine J* 2017;7:42S–52.
- 22 Fehlings MG, Tetreault LA, Riew KD, *et al.* A clinical practice guideline for the management of degenerative cervical myelopathy: introduction, rationale, and scope. *Global Spine Journal* 2017;7:21S–7.
- 23 Fehlings MG, Tetreault LA, Riew KD, *et al.* A clinical practice guideline for the management of patients with degenerative cervical myelopathy: recommendations for patients with mild, moderate, and severe disease and Nonmyelopathic patients with evidence of cord compression. *Global Spine J* 2017;7:70S–83.
- 24 Kato S, Nouri A, Reihani-Kermani H, *et al.* Postoperative resolution of magnetic resonance imaging signal intensity changes and the associated impact on outcomes in degenerative cervical myelopathy: analysis of a global cohort of patients. *Spine* 2018;43:824–31.
- 25 Meyer F, Börm W, Thomé C. Degenerative cervical spinal stenosis: current strategies in diagnosis and treatment. *Dtsch Arztebl Int* 2008;105:366–72.
- 26 Lawrence BD, Shamji MF, Traynelis VC, *et al.* Surgical management of degenerative cervical myelopathy: a consensus statement. *Spine* 2013;38:S171–2.
- 27 Kato S, Ganau M, Fehlings MG. Surgical decision-making in degenerative cervical myelopathy - Anterior versus posterior approach. *J Clin Neurosci* 2018;58:7–12.
- 28 Fehlings MG, Santaguida C, Tetreault L, *et al.* Laminectomy and fusion versus laminoplasty for the treatment of degenerative cervical myelopathy: results from the AOSpine North America and international prospective multicenter studies. *Spine J* 2017;17:102–8.
- 29 Ganau M, Holly LT, Mizuno J, *et al.* Future directions and new technologies for the management of degenerative cervical myelopathy. *Neurosurg Clin N Am* 2018;29:185–93.
- 30 Tetreault L, Ibrahim A, Côté P, *et al.* A systematic review of clinical and surgical predictors of complications following surgery for degenerative cervical myelopathy. *J Neurosurg Spine* 2016;24:77–99.
- 31 Oh T, Lafage R, Lafage V, *et al.* Comparing quality of life in cervical spondylotic myelopathy with other chronic debilitating diseases using the short form survey 36-Health survey. *World Neurosurg* 2017;106:699–706.
- 32 Fehlings MG, Tetreault LA, Kurpad S, *et al.* Change in functional impairment, disability, and quality of life following operative treatment for degenerative cervical myelopathy: a systematic review and meta-analysis. *Global Spine J* 2017;7:53S–69.
- 33 Tetreault L, Palubiski LM, Kryshchuk M, *et al.* Significant predictors of outcome following surgery for the treatment of degenerative cervical myelopathy: a systematic review of the literature. *Neurosurg Clin N Am* 2018;29:p. 115–127.
- 34 Behrbalk E, Salame K, Regev GJ, *et al.* Delayed diagnosis of cervical spondylotic myelopathy by primary care physicians. *Neurosurg Focus* 2013;35:E1.
- 35 Queckenstedt PD. Zur diagnose Der Rückenmarkskompression. *Deutsche Zeitschrift für Nervenheilkunde* 1916;55:325–33.
- 36 Guttmann L. Physiologie und Pathologie der Liquormechanik und Liquordynamik, in Allgemeine Neurologie VII/2: Allgemeine Symptomatologie Einschl. In: Bumke O, Foerster O, eds. *Untersuchungsmethoden V/2 liquor · Hirnpunktion Röntgenologie*. Berlin, Heidelberg: Springer Berlin Heidelberg, 1936: 1–114.
- 37 Stookey B. Adhesive spinal arachnoiditis simulating spinal cord tumor. *Arch Neurol Psychiatry* 1927;17:151–78.
- 38 Magnaes B, Hauge T. Surgery for myelopathy in cervical spondylosis: safety measures and preoperative factors related to outcome. *Spine* 1980;5:211–4.
- 39 Turner O, Byrne VC. The Queckenstedt test: a consideration of the method of application and nursing problems related to it. *Yale J Biol Med* 1940;12:737–41.
- 40 Kaplan L, Kennedy F. The effect of head posture on the manometrics of the cerebrospinal fluid in cervical lesions: a new diagnostic test. *Brain* 1950;73:337–45.
- 41 Da Bang EC. Revised Queckenstedt test; with special reference to the diagnosis of cervical disc protrusions. *Acta Psychiatr Neurol Scand* 1955;30:1–10.
- 42 Tachibana S, Iida H, Yada K. Significance of positive Queckenstedt test in patients with syringomyelia associated with Arnold-Chiari malformations. *J Neurosurg* 1992;76:67–71.
- 43 Kwon BK, Curt A, Belanger LM, *et al.* Intrathecal pressure monitoring and cerebrospinal fluid drainage in acute spinal cord injury: a prospective randomized trial. *J Neurosurg Spine* 2009;10:181–93.
- 44 Squair JW, Bélanger LM, Tsang A, *et al.* Spinal cord perfusion pressure predicts neurologic recovery in acute spinal cord injury. *Neurology* 2017;89:1660–7.
- 45 Chen S, Smielewski P, Czosnyka M, *et al.* Continuous monitoring and visualization of optimum spinal cord perfusion pressure in patients with acute cord injury. *J Neurotrauma* 2017;34:2941–9.
- 46 von Elm E, Altman DG, Egger M, *et al.* The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
- 47 Eskuchen K. Die diagnose des Spinalen Subarachnoidalblocks. *Klin Wochenschr* 1924;3:1851–5.
- 48 Rossini PM, Burke D, Chen R, *et al.* Non-Invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;126:1071–107.
- 49 Rossi S, Hallett M, Rossini PM, *et al.* Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39.
- 50 Taylor AR. Fallacies in interpretation of Queckenstedt's test. *Lancet* 1960;2:1001–4.
- 51 Stratford J. The Queckenstedt test and lumbar puncture. *Can Med Assoc J* 1962;86:1079.
- 52 Shibuya R, Yonenobu K, Koizumi T, *et al.* Pulsatile cerebrospinal fluid flow measurement using phase-contrast magnetic resonance imaging in patients with cervical myelopathy. *Spine* 2002;27:1087–93.
- 53 Bae YJ, Lee JW, Lee E, *et al.* Cervical compressive myelopathy: flow analysis of cerebrospinal fluid using phase-contrast magnetic resonance imaging. *Eur Spine J* 2017;26:40–8.
- 54 Rindler RS, Chokshi FH, Malcolm JG, *et al.* Spinal diffusion tensor imaging in evaluation of preoperative and postoperative severity of cervical spondylotic myelopathy: systematic review of literature. *World Neurosurg* 2017;99:150–8.
- 55 Ganau M, Syrmos N, Martin AR, *et al.* Intraoperative ultrasound in spine surgery: history, current applications, future developments. *Quant Imaging Med Surg* 2018;8:261–7.
- 56 Etz CD, Di Luozzo G, Zoli S, *et al.* Direct spinal cord perfusion pressure monitoring in extensive distal aortic aneurysm repair. *Ann Thorac Surg* 2009;87:1764–74.
- 57 Bower TC, Murray MJ, Glivoczki P, *et al.* Effects of thoracic aortic occlusion and cerebrospinal fluid drainage on regional spinal cord blood flow in dogs: correlation with neurologic outcome. *J Vasc Surg* 1989;9:135–44.
- 58 Griffiths IR, Pitts LH, Crawford RA, *et al.* Spinal cord compression and blood flow. I. The effect of raised cerebrospinal fluid pressure on spinal cord blood flow. *Neurology* 1978;28:1145–51.
- 59 Kazama S, Masaki Y, Maruyama S, *et al.* Effect of altering cerebrospinal fluid pressure on spinal cord blood flow. *Ann Thorac Surg* 1994;58:112–5.
- 60 Walters BC, Hadley MN, Hurlbert RJ, *et al.* Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. *Neurosurgery* 2013;60:82–91.
- 61 Saadeh YS, Smith BW, Joseph JR, *et al.* The impact of blood pressure management after spinal cord injury: a systematic review of the literature. *Neurosurg Focus* 2017;43:E20.

- 62 Werndle MC, Saadoun S, Phang I, *et al.* Monitoring of spinal cord perfusion pressure in acute spinal cord injury: initial findings of the injured spinal cord pressure evaluation study\*. *Crit Care Med* 2014;42:646–55.
- 63 Saadoun S, Chen S, Papadopoulos MC. Intraspinal pressure and spinal cord perfusion pressure predict neurological outcome after traumatic spinal cord injury. *J Neurol Neurosurg Psychiatry* 2017;88:452–3.
- 64 Werndle MC, Saadoun S, Phang I, *et al.* Measurement of intraspinal pressure after spinal cord injury: technical note from the injured spinal cord pressure evaluation study. *Acta Neurochir Suppl* 2016;122:323–8.
- 65 Phang I, Zoumprouli A, Papadopoulos MC, *et al.* Microdialysis to optimize cord perfusion and drug delivery in spinal cord injury. *Ann Neurol* 2016;80:522–31.